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Translation

PATENT COOPERATION TREA

PCT/JP2003/010303

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 02-F-049PCT	FOR FURTHER ACTION See Form PCT/IPEA/416	
International application No. PCT/JP2003/010303	International filing date (*day/month/year*) 13 August 2003 (13.08.2003)	Priority date (*day/month/year*) 16 August 2002 (16.08.2002)
International Patent Classification (IPC) or national classification and IPC A61K 39/04, 39/00, C12N 15/11, 15/31		
Applicant JAPAN SCIENCE AND TECHNOLOGY AGENCY		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

3. This report is also accompanied by ANNEXES, comprising:

   a. ☐ *(sent to the applicant and to the International Bureau)* a total of _____ sheets, as follows:

      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).

      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the report
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15 March 2004 (15.03.2004)	15 October 2004 (15.10.2004)
Name and mailing address of the IPEA/JP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2003/010303

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language _____, which is language of a translation furnished for the purpose of:

☐ international search (under Rules 12.3 and 23.1(b))

☐ publication of the international application (under Rule 12.4)

☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☒ The international application as originally filed/furnished

☐ the description:

pages _____, as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☐ the claims:

pages _____, as originally filed/furnished

pages* _____, as amended (together with any statement) under Article 19

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☐ the drawings:

pages _____, as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRE[redacted]NARY REPORT ON PATENTABILITY

I[redacted]tional application No.
PCT/JP03/10303

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1, 2	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1, 2	NO
Industrial applicability (IA)	Claims	1, 2	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Document 1: Microbiology, April 1996, Vol. 142, No. 4, pages 915-925
Document 2: Infection and Immunity, January 1989, Vol. 57, No. 1, pages 283-288
Document 3: Lectures on New Biochemical Experiments (Vol. 1), Proteins VII - Protein Engineering - (in Japanese), The Japanese Biochemical Society, Tokyo Kagaku Dozin Co., Ltd., 15 February, 1993 (15.02.93), pages 314-315
Document 4: Nature, 11 June, 1987 (11.07.87), Vol. 327, No. 6122, pages 532-535
Document 5: JP, 4-500305, A (Whitehead Institute for Biomedical Research), 23 January, 1992 (23.01.92), & WO, 90-00594, A2
Document 6: JP, 3-72888, A (Ajinomoto Co., Inc.), 28 March, 1991 (28.03.91), & EP, 400973, A1
Document 7: JP, 4-506297, A (Whitehead Institute for Biomedical Research), 5 November 1992 (05.11.92), & WO, 90-15873, A1
Document 8: JP, 6-501607, A (Albert Einstein College of Medicine of Yeshiva University), 24 February, 1994 (24.02.94), & WO, 92-01783, A1

Claims 1 and 2

The subject matters of claims 1 and 2 do not appear to involve an inventive step in view of documents 1-4 cited in the ISR and documents 5-8 that are family members of documents cited in the ISR.

Documents 1 and 2 respectively describe (especially see the abstracts of both the documents) that (1) the gene of the attenuated BCG strain (hereinafter called "BCG") of *Mycobacterium bovis* has a high G+C content, and (2) the probability that the third base of each codon in its code area is G or C is high. Furthermore, it is publicly known that using a codon highly frequently used in a host for expressing an extrinsic protein is important for expressing the intended protein in a large amount, as also described in document 3 (see page 315, upper column). Moreover, the BCGs capable of expressing extrinsic proteins are publicly known, as also described in documents 4-8, and they are used as vaccines.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: V2

Meanwhile, conventional recombinant BCG vaccines are not sufficient in immune inducibility (the applicant also describes this matter in the third paragraph of "Background Art" in the specification). Furthermore, increasing the inoculation amount of an antigen for enhancing the immune inducibility in the case where the immune induction by a vaccine is not sufficient is a commonly used means in this technical field, like selecting an adequate adjuvant, adjusting vaccine inoculation times or intervals, etc.

So, it is considered to be obvious for a person skilled in the art (1) to substitute G or C for the third base of each of the codons of a polynucleotide encoding an extrinsic protein in a recombinant BCG without changing its amino acids, for increasing the expression of the extrinsic protein for the purpose of enhancing the immune inducibility of the recombinant BCG vaccine, and (2) to let the polynucleotide encoding the extrinsic protein contain a large amount of G or C, without changing its amino acids.